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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/052,092	01/18/2002	Suzanne Fuqua	HO-P02102US2	5838

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EXAMINER
SWITZER, JULIET CAROLINE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,092	FUQUA ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *1-3,11,15,21 and 23-63* is/are withdrawn from consideration.

5)☒ Claim(s) *7-9* is/are allowed.

6)☒ Claim(s) *3-6, 10, 12-14, 16-20, 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group III, claims 3-10, 12-14, 16-20, and 22, further electing species SEQ ID NO: 15 in the paper filed 4/23/03 is acknowledged. Claims 1-3, 11, 15, 21, and 23-63 are withdrawn from prosecution.

Information Disclosure Statement

2. All of the references listed on the 1449 filed 10/29/02 have been considered. The reference by McDonnell *et al.*, designated as CB1 on the 1449, has been lined through because it does not contain a proper citation as the citation does not include a date. If applicant wishes for this reference to appear on the front of any eventually issued patent, a new 1449 should be submitted which provides a proper citation for this reference.

Drawings

3. New corrected drawings are required in this application because in Figure 2 the boxes are not around the appropriate nucleotide and amino acid as is indicated by the description of the drawings, and thus the drawing is confusing. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 5-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the limitation "said premalignant lesion" in line 6 of the claim. There is insufficient antecedent basis for this limitation in the claim. The claim does not previously recite a premalignant lesion. Claim 6 is rejected because it depends from claim 5.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 3, 4, 10, 12, 13, 14, 16, 17, 18, 19, 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining a predisposition to the development of breast cancer or invasive breast cancer, wherein the presence of an A908G mutation in the nucleic acid sequence for an estrogen receptor alpha is indicative of a predisposition to developing breast cancer or invasive breast, does not reasonably provide enablement for methods of diagnosis of beast cancer or methods of classifying breast cancer in an individual. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Breadth of the Claims

The rejected claims each recited method steps which set forth that the presence of an A908G mutation in an estrogen receptor alpha nucleic acid sequence is indicative of the presence of breast cancer or invasive breast cancer, in particular. That is, the claims lead the practitioner to draw the conclusion that breast cancer, or invasive breast cancer in particular, is present when the particular mutation is present.

State of the Art

Fuqua *et al.* (Cancer Research 60, 4026-4029) reports an A to G transition at nucleotide 908 of the estrogen receptor alpha gene, and further teaches that this alteration was found in 18 of 55 premalignant lesions (p. 4027). It is to be noted that Fuqua *et al.* have some authors in common with the inventors of the instant application but have a different inventive entity per se. Further, the experiments presented by Fuqua *et al.* in the journal article are also presented in the examples of the instant specification. Fuqua *et al.* further teach that "hyperplasias are relatively common in the breast, and only a small fraction of them will progress to cancer (p. 4029)." Fuqua *et al.* do not test actual breast cancer tissue for the presence of the mutation, they only test hyperplasias, which by definition are not cancer.

Guidance and Examples in the Specification

The specification does not provided any examples which definitively support the assertions that (a) when the A908G mutation is present breast cancer is present or (b) when the mutation is present in a cancer cell invasive breast cancer is present. To the contrary, the specification provides numerous examples of cases where the mutation is present in non-cancer tissues.

The specification teaches a novel A908G mutation in the fifth exon of the estrogen receptor gene, and further teach that this mutation causes a coding change where normal type receptors have a lysine at amino acid 303 of the receptor and mutated forms have an arginine at this position. The specification teaches that the mutation is present in 34% of 59 total cell samples taken from hyperplasias of the breast, and that the mutation appeared in normal adjacent breast tissue of some of the samples tested (Example 5). Thus, the specification demonstrates that the A908G mutation is present in samples where cancer is not present, as hyperplasia tissue and adjacent normal breast tissue are in fact not cancerous tissues. Applicant has not provided any data or evidence that suggests that each time the A908G mutation is present the hyperplasia or adjacent normal breast tissue develops into breast cancer, or invasive breast cancer as some of the claims recite. Example 10 shows that the A908G mutation was present in 62% of invasive breast cancer samples tested, however neither this example nor any other example in the specification tests a population of non-invasive breast cancers to determine the frequency of the mutation in non-invasive breast cancers. Therefore, lacking this critical control information, it is not possible to determine if in fact the presence of the mutation in a cancer cell is a clear indicator of the presence of invasive versus non-invasive breast cancer.

Level of Unpredictability and Level of Skill in the Art

There is no known way to predict *a priori* if a given hyperplasia or breast cancer tumor will in fact develop into a breast cancer tumor or invasive breast cancer in particular. It is thus highly unpredictable as to whether or not the A908G mutation taught herein is in fact an indication that in fact a given hyperplasia will develop into breast cancer, or that a given breast cancer will be an invasive breast cancer. Any conclusion to that effect based on the evidence in

the specification is not fully supported because the specification does not provide evidence that the presence of the mutation will necessarily result in the development of invasive breast cancer. While the level of skill in the art is quite high, the unpredictability in the prior art with regard to the ability to conclude that a given mutation will lead to the presence of breast cancer, or invasive breast cancer is higher.

Quantity of Experimentation

In order to practice the claimed invention, the one would have to undertake many further experiments to determine what percentages of hyperplasias and related normal tissues that have the mutation do in fact develop into breast cancer and invasive breast cancer in particular. In order to practice methods of classifying cancer cells as invasive breast cancer cells, one would have to sample hundreds of patients in order to determine whether or not the A908G mutation in the estrogen receptor alpha is in fact present in non-invasive types of breast cancers. Such experiments that would be necessary to provide the critical data necessary to practice the invention would be complicated, time consuming and require the assaying of hundreds of patients.

Conclusion

Upon considering all of these factors, it is concluded that it would require undue experimentation to practice the claimed invention commensurate in scope with the claims. Namely, this conclusion is drawn due to the high level of unpredictability in the art, the lack of working examples with regard to the claimed invention, the high quantity of experimentation necessary to practice the invention, and the breadth of the claims which lead the practitioner to conclude that cancer is present in a sample or invasive breast cancer is present in a sample

merely due to the presence of a mutation that has been shown to be present in non-malignant tissue as well as in malignant tissues.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kimoto (GenBank Accession E13443, GI: 3252248) in view of Stratagene Catalog, 1988.

Kimoto teaches a primer which comprises instant SEQ ID NO: 15. In particular, nucleotides 1 to 20 of instant SEQ ID NO: 15 are identical to the complement of nucleotides 1 to 20 of the primer taught by Kimoto.

Kimoto does not teach the primer in a kit.

Stratagene teaches gene characterization kits and the benefits of such kits.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the primer taught by Kimoto in a kit for the amplification of a portion of the estrogen receptor alpha gene. The ordinary practitioner would have been motivated to have produced such a kit because since the Stratagene catalog expressly teaches the benefits to the practitioner of kits:

> "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, pre-mixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control."

It is noted that these claims contain a preamble which recites an intended use, however, it is also noted that this use does not confer patentable weight on the product claims since the preamble does not materially change what is present in the kit itself and thus represents an intended use of the kit (see MPEP 2111.02). Therefore, the kits of the instant claims are *prima facie* obvious over the disclosure of Kimoto in view of the Stratagene catalog.

Furthermore, it is note that the instant claims are currently drawn using open "comprising" type language, and thus this language has been interpreted to mean that the primers included in the claimed kits encompass primers that comprise the recited sequence, allowing for the addition of nucleotides onto the ends. However, it is noted that even if the claims were amended to limit the kit to containing a primer consisting of instant SEQ ID NO: 15, at the time the invention was made it was a matter of routine optimization to add or subtract nucleotides

from the ends of known primers in order to provide functionally equivalent primers for the amplification of a target sequence.

Conclusion

11. Claims 7-9 are allowed. The closest prior art, Fuqua *et al.* fails do demonstrate that the A908G mutation in the estrogen receptor alpha gene is present in invasive breast cancer. Thus, they do not teach a method of detecting a susceptibility to development of invasive breast cancer. Claims 5-6 are free of the prior art and would be allowable if the rejections under 112 2nd paragraph were overcome.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Switzer
Examiner
Art Unit 1634

June 26, 2003